

Advances in Pain Research
Highlights of the First NIH Pain Consortium Symposium
April 17-18, 2006
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INTRODUCTION

Founded in 1996, the NIH Pain Consortium comprises 20 institutes and centers at NIH that share common goals: developing a comprehensive NIH pain research agenda, identifying key opportunities for interdisciplinary research, increasing NIH visibility in pain research, and pursuing private sponsorship. In April 2006, the Pain Consortium held its first symposium, drawing experts from the US and Canada to report on current research into the etiology and treatment of pain.

Among Symposium attendees were members of the American Pain Society, a multidisciplinary organization of basic scientists, social scientists, and clinicians whose goal is to increase knowledge about pain and to transform public policy to reduce pain-related suffering.

The symposium was organized by Linda L. Porter, PhD, Program Director, National Institute of Neurological Disorders and Stroke; John Kusiak, PhD, Program Director, National Institute of Dental and Craniofacial Research; Kathy Mann Koepke, PhD, Program Director, National Institute of Nursing Research; and Wendy Smith, MA, PhD, Deputy Director, Office of Cancer Complementary and Alternative Medicine, National Cancer Institute.

In Session 1, Genetics and Pain, two presentations summarized results of experimental genetic methods that have been utilized to trace a specific neural pain pathway in mammals and to transfer genes that can provide pain relief. A third presentation discussed genetic correlates of high-sensitivity and low-sensitivity to pain.

In Session 2, Neuronal and Glial Mechanisms of Pain, the role of inflammatory molecules released by activated glial cells was reviewed. Polyneuropathies associated with HIV infection were then discussed, followed by the genetic control of nociceptor differentiation.

In Session 3, The Role of Imaging in Pain Research, cortical brain areas involved in the processing and perception of pain were reviewed, and the effects of expectation, attention, and mood were discussed.

In Session 4, Cognitive and Emotional Aspects of Pain, ethnic and gender differences in the individual response to pain, catastrophizing, and the strong effects of placebos were discussed.

In Session 5, Headache, the possibility that migraines may be the result of ion channel dysfunction was reviewed along with research on cortical spreading depression and familial hemiplegic migraine. The progressive development of migraine headaches along with treatment options were then discussed.

In Session 6, Cancer Pain: Research and Interventions, the role of cells that destroy bone in the development of cancer bone pain was presented, along with new effective therapies for cancer pain based on interfering with their activity. The results of a randomized trial that used psychoeducational interventions to help patients manage pain were summarized.

In Session 7, Novel Therapies for Pain, two exotic sources for developing new pain medications were discussed; these are venoms from marine cone snails and a toxin purified from latex secreted by the Moroccan plant *Euphorbia resinifera*. A new MRI approach was presented that teaches patients to modify their brain activity to control pain.

In Session 8, Junior Investigator Presentations, studies investigating pain and strength loss due to deep tissue damage, modulation of pain by tumor necrosis factor α , and allodynia [where innocuous stimuli now produce pain] caused by nucleoside reverse transcriptase inhibitors (NRTI) were presented.

Brief summaries of each presentation may be found below, as well as a brief glossary.

Glossary of Terms

Terms	Definition
Allodynia	Pain in response to previously innocuous stimuli
Catatrophizing	Cognitive response to pain characterized by anxiety, hypervigilance, and helplessness
GDNF	Glial derived growth factor
Glial cell	Brain cells that are not nerve cells with a variety of supportive functions
Neuropathic pain	Pain due to damage to nerve cells
NGF	Nerve growth factor
Nociceptor	Nerve cells that transmit information about pain

I. GENETICS AND PAIN

*Moderator: John Kusiak, PhD, National Institute of Dental and Craniofacial Research
Pain Consortium Representative*

A Genetic Approach to Tracing Pain Transmission Circuits

Allan Basbaum, PhD, University of California, San Francisco

Nociceptors are nerve cells that transmit information about pain. One type of nociceptor responds to a growth factor called nerve growth factor [NGF] and uses peptide molecules to transmit information to the brain. A second type of nociceptor responds to a different growth factor, glial derived nerve factor [GDNF], and does not use peptide molecules. The GDNF class of nociceptors uses a special type of sodium channel, the NaV1.8 channel. The entire pathway of the GDNF nociceptor was discovered using a tracer [wheat germ agglutinin] linked to the NaV1.8 gene. The GDNF nociceptor enters the spinal cord and ends in a deep layer of the spinal cord. The next nerve cells in the pathway stay in the spinal cord and communicate with nerve cells [in lamina V] that send information to the brain. Surprisingly, the areas of the brain that receive information from the GDNF nociceptor pathway are associated with emotions [hypothalamus and amygdale] and with motor control [globus pallidus] rather than those areas that are more traditionally associated with pain [somatosensory cortex]. This new finding may help to explain chronic pain, which appears to be a different process from acute pain and which is not well understood.

Gene Transfer to the DRG for the Treatment of Pain

David Fink, MD, University of Michigan, Ann Arbor

The undesirable side effects of currently available pain medications might be circumvented if the drugs could be targeted selectively to nociceptor cells. A possible delivery system would be to use the herpes simplex virus (HSV), which is naturally taken up by sensory nerve cells, including nociceptor cells. To test this delivery system, an experimental HSV vector that can not replicate was engineered to produce enkephalin, the naturally occurring ligand for the opiod receptor. The experimental vector was inoculated into the foot pads of rats. A reduction in pain was observed in several experimental models for inflammatory pain, neuropathic pain, or bone cancer pain. Pain relief persisted for up to 28 days following inoculation. As the relief diminished, a second inoculation could re-establish pain relief. Other genes that have been inserted into the experimental HSV vector were endomorphin-2, the ligand for the mu-opiod receptor, and GAD-67, the enzyme (glutamic acid decarboxylase) that catalyzes the production of GABA from glutamic acid. All were effective in reducing pain in various pain models. This research is now ready for human trials and plans for a Phase I trial are underway.

Genetic Basis for Development of Chronic Pain Conditions

Luda Diatchenko, MD, PhD, University of North Carolina, Chapel Hill

Chronic pain is a multidimensional disease. Susceptibility to the development of chronic pain was assessed for temporomandibular disorder [TMD], one form of chronic pain. In 200 otherwise healthy subjects, basal sensitivity to pain was highly variable. Those who were most sensitive to pain were 2.7 times more likely to get TMD than those who were least sensitive. Other risk factors for developing TMD were low blood pressure and negative psychological characteristics; for example, subjects with high anxiety were 5.5 times more likely to get TMD.

In TMD patients, a gene that was highly associated with pain perception was the gene for catecholamine transferase (COMT). Three genetic haplotypes of COMT occur naturally in humans and correlate with low, average, or high sensitivity to pain. Subjects who were heterozygous for COMT haplotype 2 and haplotype 3 (low COMT activity) were more sensitive to pain and were 2.3 times more likely to develop TMD. The activity of COMT in pain perception is ultimately mediated through beta-2 and beta-3 adrenergic receptors. The beta-2 adrenergic receptor is activated in persistent pain states and in psychological distress; resulting in increased production of inflammatory molecules. Of the 3 haplotypes for the beta-2 adrenergic receptor, haplotype 2, characterized by receptors with high-level expression and low internalization rate, is associated with higher sensitivity to pain.

II. NEURONAL AND GLIAL MECHANISMS OF PAIN

Moderator: David Thomas, PhD, National Institute on Drug Abuse Pain Consortium Representative

Activated Glia: Culprits in Neuropathic Pain, Opioid Tolerance, and Opioid Dependence

Linda Watkins, PhD, University of Colorado, Boulder

Glial cells are brain cells that are not nerve cells, and have a variety of supportive functions. While nerve cells transmit pain information, the supporting glial cells are also important in pain processing. When glial cells are activated by inflammation, tissue injury, or chemotherapy, they release various inflammatory molecules, particularly interleukin-1 (IL-1). Injection of agents that block IL-1 activity, or injections of AV411, an experimental molecule that blocks glial activation, can reduce pain. Neuropathic pain, experimentally induced in rats by chronic nerve constriction, was reduced when such blockers were injected into the spinal cord. Interleukin-10 [IL-10], an interleukin that shuts down production of all inflammatory cytokines, was also effective in reducing neuropathic pain. IL-10 was injected into the rat spinal cord as naked DNA (no vector). After 2 closely spaced injections of naked IL-10 DNA, pain relief was long-lasting (3 months) and re-injection after 3 months continued to produce relief.

Fractalkine, a unique molecule released by nerve cells when they are injured, binds to receptors that are expressed on a subset of glial cells (microglia). The response to fractalkine may be an important component of glial cell activation after injury to nerve

cells. Opioids also activate glial cells, leading to glial cell release of IL-1. Activation of glial cells counteracts the analgesic effects of opioids and may also explain the development of opioid tolerance and drug reward. As the glial opioid receptor appears to be different from the neuronal opioid receptor, development of morphine analogs that do not activate glial cells may avoid some of the current drawbacks of opioid use.

HIV and Painful Peripheral Neuropathy

Justin McArthur, MBBS, MPH, Johns Hopkins University, Baltimore

Two sensory neuropathies are commonly associated with long-term HIV infection, a distal sensory polyneuropathy (caused by the HIV virus) and an antiretroviral polyneuropathy (caused by treatments given for HIV). The clinical manifestations of the two polyneuropathies, which affect the feet most often, are identical even though the causes are dissimilar. The HIV virus affects perivascular macrophages, and it is thought that activation of macrophages in dorsal root ganglia ultimately leads to axonal degeneration and development of neuropathy. HIV treatments are now being taken for longer periods of time, and it has become clear that the medications themselves (eg, d4T and DDI) can produce neuropathy, perhaps through mitochondrial toxicity.

Currently, 40% of HIV positive patients report neuropathy. Skin punch biopsy samples (3 mm punch) were obtained and epidermal nerve fiber density was quantified. Samples from HIV positive patients who have not developed neuropathy had a lower density of nerve fibers compared with samples from normal subjects. Samples from HIV positive patients who had neuropathy were even lower, and samples from diabetic patients with neuropathy exhibited the lowest nerve densities. When capsaicin was applied in the punch site, some nerve cells were killed, and the subsequent regeneration of nerve fibers could be monitored. Comparison of HIV positive patients with normal subjects indicated that HIV positive patients have a decreased regenerative ability.

Runx1 Determines Nociceptor Phenotype Necessary for Thermal and Neuropathic Pain

Qiufu Ma, PhD, Dana-Farber Cancer Institute and Harvard Medical School, Boston

Nociceptors are a heterogeneous group of nerve cells that express a large number of different ion channels and receptors. How is the expression of nociceptor molecular diversity controlled? To answer this question, a library of transcription factors was screened for spatial expression. Three transcription factors were specific to nociceptors in spinal dorsal root ganglia. One of these, *Runx1*, defines a class of nociceptors and is also involved in human leukemias and in T cell differentiation.

Runx1 is expressed by all nociceptors early in development. *Runx1* then becomes restricted to the class of nociceptors that do not use peptide neurotransmitters and are dependent on the growth factor GDNF. *Runx1* mutants missing this class of nociceptors have a normal response to mechanical pain, but do not respond to heat or cold pain. They also do not develop allodynia in response to sciatic nerve section. Thus, *Runx1* seems to be part of a coherent genetic program that controls the development of a class of nociceptors involved in neuropathic pain.

III. THE ROLE OF IMAGING IN PAIN RESEARCH

Moderator: Richard Nahin, PhD, MPH, National Center for Complimentary and Alternative Medicine Pain Consortium Representative

fMRI of Trigeminal Pain Pathways in Health and Disease

David Borsook, MD, PhD, McLean Hospital, Belmont

During the development of a migraine headache, changes in sensitization occur throughout the body. If hypersensitivity is restricted to the face, this localized allodynia is mediated primarily by trigeminal sensory nerve cells. If the allodynia is generalized to the entire body, then changes in activity are also seen in the brain, specifically the thalamus.

Subjects with right-sided V2 neuropathy have chronic pain in the V2 region on the right side of their face. They were stimulated with brush, cold, or heat, applied to both sides of the face and to the V2 and V3 regions. Functional MRI imaging showed a difference in activation areas of the brainstem that are involved in emotions [ventral tegmentum and substantia nigra], in modularity systems [pontine nuclei, periaqueductal gray], and in sensory motor response [red nucleus]. Changes in higher brain regions were found in the striatum, hippocampus, and frontal regions.

Neural Correlates of the Subjective Experience of Pain

Robert Coghill, PhD, Wake Forest University, Winston-Salem

Pain is a highly subjective response. From a neurological point of view, the personal experience of pain is best described as a top-down process. The highest cortical levels of the brain combine objective sensory information from the body with other cognitive information and personal experiences to produce an individualized experience of pain. For example, normal healthy subjects rated the same pain stimulus (heat on the leg) on a scale from 1 to 10, with scores ranging from 1.05 (“I thought this would hurt”) to 8.9 (“I couldn’t have stood anymore”). Imaging the brains of these subjects showed that certain cortical brain areas (primary somatosensory cortex, anterior cingulate cortex, and anterior insular cortex) were more active in brains of subjects with high sensitivity to pain compared with low sensitivity subjects. However, no difference in activity was seen in subcortical brain areas (thalamus) between the two groups.

Since factors such as past experience and future predictions influence pain, the role of expectation was investigated. Subjects were trained in an experiment in which they heard a tone and, after a pause, received a heat pulse. Lower heat levels were delivered after short pauses and higher heat levels after longer pauses. However, subjects were sometimes randomly given the high heat level after a short pause instead of after a long pause. Subjects experienced less pain when they received high heat after a short pause, based on self reports and on brain scans. Thus, expectations powerfully shape the experience of pain.

Effects of Attention and Emotion on Pain Perception

M. Catherine Bushnell, PhD, McGill University, Montreal

Processing of pain is affected by both attention and mood. To examine the effect of attention, subjects were presented with both a pain stimulus and an auditory stimulus. If subjects were instructed to pay attention to the auditory stimulus (distinguishing between two tones), activity in primary somatosensory cortex where pain processing occurs was decreased. This effect is not specific to pain. In general, attention to one sensory modality increases activation in that modality and decreases activation in others.

An olfactory stimulus was used to examine the effect of emotions. Odors have a strong emotional component. Most odors are perceived as good or bad, while few are perceived as neutral. Bad odors put the subjects in a bad mood, and their pain unpleasantness rating was high, irrespective of whether they were paying attention to pain stimuli or odor stimuli. Olfactory stimuli led to changes in brain activity (cingulate cortex, primary and secondary somatosensory cortex, insular cortex). As some of these areas were the same as the brain areas affected by attention, mood state and attentional state have overlapping influences on the experience of pain.

IV. COGNITIVE AND EMOTIONAL ASPECTS OF PAIN

Moderator: Ray Dionne, DDS, PhD, National Institute of Nursing Research Intramural Research Director

Individual Differences in Pain and Analgesia: Genes, Gender, and Ethnicity

Roger Fillingim, PhD, University of Florida, Gainesville

Why do individual differences matter? Tissue damage is actually a poor predictor of pain, and treatment outcomes are highly variable. Understanding individual variability might make it possible to predict development of chronic pain and response to particular therapies. Data were collated and analyzed from 13 different pain models, including ischemic pain, heat pain, pressure pain, and temporal summation of heat pain. Sensitivity to one type of pain was not correlated with sensitivity to a different type. Women and ethnic minorities tended to cluster in the high pain-sensitive groups. Differences in sensitivity between ethnic groups were more pronounced at suprathreshold pain responses.

Sex- and race-dependent associations with analgesia may involve the mu-opioid receptor. Individuals with a rare allele (the G allele), especially men, are less sensitive to pressure pain. This rare allele is difficult to find in African Americans. In non-Hispanic whites, this rare allele is reported to confer lower pain sensitivity, while in Hispanics this rare allele confers higher pain sensitivity. Sex differences have also been reported in the response to kappa opioid analgesia which is associated with the melanocortin-1 gene. Since people with red hair express various polymorphisms of melanocortin-1, the gene was sequenced to identify people who were genetic redheads. Women with the melanocortin-1 polymorphism had a greater analgesic response to the kappa opioid pentazocine, but the response in men was not affected by the gene.

Cognitive Factors That Enhance Pain Processing

Jennifer Haythornthwaite, PhD, Johns Hopkins University, Baltimore

How people respond to pain is influenced by a wide variety of factors, including genetics, personality, beliefs, stress, mood, neuroendocrine function, and sleep patterns.

Catastrophizing is a cognitive response to pain that is characterized by anxiety (negative emotions: “I worry that it will never end”), hypervigilance (paying attention to pain: “I can’t keep it out of my mind”), and helplessness (beliefs about pain: “I’m afraid it will get worse”). Men tend to catastrophize less than women do. Higher levels of catastrophizing are consistently correlated with pain, although catastrophizing does actually correlate with pain scores on a muscle palpitation test. The relationship between catastrophizing and pain is independent of negative mood. Catastrophizing at one point in time is a good predictor for development of pain at a later point in time.

Catastrophizing interferes with pain coping strategies, since it is highly correlated with what people think they can do. Catastrophizing undermines an individual’s perception of control, their ability to self-advocate, and it predicts difficulty with distraction and attentional coping strategies. High catastrophizers receive about twice as much analgesics as low catastrophizers. Treatments to reduce pain may reduce catastrophizing, although the pain itself and the cognitive response to it are not always associated.

The Placebo Effect: New Insights

Ted Kaptchuk, OMD, Harvard Medical School, Boston

In a study designed to assess the effects of placebo on pain, subjects were given either a sham pill or a sham device (acupuncture) to alleviate chronic arm pain due to repetitive strain injury. The sham pill was a starch pill. The sham acupuncture device was a needle that telescoped into its own shaft rather than entering the subject’s arm.

Treatments were scored on 2 different pain scales, a grip strength test, and a practical function test. After 4 weeks both sham treatments were effective, but not in an identical fashion, suggesting that a real placebo effect exists over time. If subjects had been getting better spontaneously, or the study measured regression to the mean, the response to either sham treatment would be expected to be the same.

In a second study, 16 normal subjects were given sham acupuncture on one side of the arm or no intervention as a control on the other side of the arm. In the training session, the pain stimulus was lowered during the sham acupuncture so that the subject thought the procedure had worked. In a following visit, the procedure was repeated but the pain stimulus was the same during the sham acupuncture or no intervention. All subjects reported less pain during the sham acupuncture, which was consistent with their expectation. Imaging of their brains, subtracting pre- from post-stimulation activity and intervention from no intervention, showed that certain areas of the brain (right anterior insular, bilateral rostral anterior cingulate, and dorsolateral prefrontal cortex) were involved in modulating pain.

V. HEADACHE

Moderator: Linda Porter, PhD, National Institute of Neurological Disorders and Stroke Pain Consortium Representative

Cortical Spreading Depression: A Pain Stimulus and Target for Prophylaxis in Migraine?

Michael Moskowitz, MD, Massachusetts General Hospital, Charlestown

Cortical spreading depression (CSD) in the mammalian brain is a self-propagating depolarization that spreads at a rate of 3 to 5 mm/second and is followed by a prolonged period of low neuronal activity. CSD releases large quantities of inflammatory molecules and may play an important role in the onset of migraine headaches. Drugs that are currently used to treat migraine can suppress CSD in experimental animals but only when given for at least 4 weeks. Although the natural trigger for CSD is not known, it is a useful model for migraine and the association of CSD with familial hemiplegic migraine has led to the theory that migraines are linked to ion channel dysfunction in the brain.

An inherited type of migraine, familial hemiplegic migraine (FHM), is characterized by severe and prolonged auras and has been linked to mutations in three genes. The product of one gene, FHM1, is a calcium channel [P/Q high voltage sensing calcium channel] that is most abundant at glutaminergic synapses and is important for regulating glutamate release. Mutations of FHM1 are gain-of-function mutations in the alpha 1 subunit, which forms the pore and is voltage sensing. The product of another gene, FHM2, is a Na/K ATPase that is predominantly expressed on glial cells. Mutations of FHM2 are loss of function mutations in the alpha subunit that binds both ATP and potassium. The third gene, FHM3, is a voltage-gated Na channel. FHM3 mutations contribute to hyperexcitability by allowing nerve cells to repolarize more quickly.

Experimental mice that express the mutated FHM1 gene (R192Q) have an increased susceptibility to cortical spreading depression. A possible unifying theme is that the gain of function in the calcium channel in nerve cells or the loss of function in ATPase in glial cells both result in increased glutamate release, a known experimental trigger for CSD.

Defeating Migraine Pain: A Race Against the Development of Central Sensitization and Cutaneous Allodynia

Rami Burstein, PhD, Harvard Medical School, Boston

The response of sensory nerve cells to inflammatory molecules applied to the surface of the brain can be used to model migraine headaches. The first responders are trigeminal nerve cells in the face and head, which become sensitive to mechanical stimuli about 15 minutes after application of inflammatory molecules. This unusual sensitivity could be one factor leading to the throbbing pain associated with headaches. As a migraine event progresses, activation of secondary nerve cells in the spinal cord occurs. Allodynia, a hypersensitivity where normally innocuous stimuli become painful, develops over the head. Approximately 2 to 3 hours after allodynia of the head starts, about half of patients develop allodynia over the whole body. Whole body allodynia is associated with activation of nerve cells in the brain [thalamic nuclei PO and VPM].

Migraine patients who do not have allodynia respond to typical migraine drugs. Most current migraine drugs are thought to affect the activity of trigeminal sensory nerve cells by decreasing vasodilation and by blocking neuronal activity in the spinal cord. Patients who develop allodynia later in the migraine will respond to migraine drugs and become painfree if they are treated early enough. This may be explained by the fact that, if the drugs are given soon enough, neuronal cells in the spinal cord do not get activated. However, if the medication is started too late, then the activation has already occurred and the medication can not reverse it. Patients who have chronic allodynia even in the absence of migraines do not respond to typical migraine medication. Animal studies suggest that administration of intravenous COX-1 and COX-2 inhibitors in combination with inhibitors of synaptic transmission may prove to be beneficial.

VI. CANCER PAIN: RESEARCH AND INTERVENTIONS

Moderator: Wendy Smith, MA, PhD, National Cancer Institute Pain Consortium Representative

Bone Cancer Pain: Causes, Consequences, and Therapeutic Opportunities

Patrick Mantyh, PhD, JD, University of Minnesota, Minneapolis

The majority of cancer patients report having bone pain. Usually the primary cancer is elsewhere and the tumor cells have metastasized to bone. Once in the bone, tumor cells can be quiescent for years, which is the reason they escape the initial rounds of chemotherapy.

Osteoclasts are special cells in the bone whose job is to break down bones. Osteoclasts are found in high numbers in tumor-bearing bone, and their activity contributes to bone cancer pain. Osteoclasts destroy bone by acidifying the environment to about pH4, which destabilizes the bone and allows the osteoclast to resorb bone material. The low pH also damages local sensory nerve cells, leading to neuropathic cancer pain.

New therapies to treat bone cancer pain include drugs that kill osteoclasts, such as OPG (a molecule that regulates osteoclast numbers) or biphosphonates (which are cytotoxic to osteoclasts). Anti-inflammatory molecules such as COX-2 inhibitors are effective in reducing pain. They also seem to slow down disease progression. A third approach, and the most effective, is to target the sensory nerve cells damaged by osteoclast activity. Injection of antibodies to nerve growth factor [a growth factor required for sensory nerve cell survival] appear to be even more effective than injections of morphine. The nerve growth factor antibodies do not kill the sensory nerve cells, since normal sensitivity is retained; but rather seems to down-regulate receptor expression.

Improving Pain Management and Patient Outcomes Through a Self-Care Intervention

Christine Miaskowski, RN, PhD, University of California, San Francisco

The benefits of teaching pain management to patients and their caregivers were assessed in a randomized, 6-week intervention trial of 200 cancer patients living in Marin County, CA who had bone pain. The control group got the AHCPR version of the Cancer Pain Guideline, kept a diary of medication intake and pain intensity scores, and were

telephoned periodically by the nurse. If they had a question about their pain, they were referred to their primary care doctor. For the intervention group, the goals were to increase knowledge about cancer pain management, engage in skills training, and provide nursing support. A 4.5 hour training session at the beginning of the study was individualized to each patient based on answers to a questionnaire. The intervention group also received a pillbox, a diary, and a short script to use when talking to their physician. The intervention group was seen with the same frequency as the control group.

By a variety of different measures the intervention was effective: overall knowledge increased, pain intensity scores decreased, and intake of analgesics increased. However, adherence to prescribed pain prescriptions in both groups was dependent on the dosing regimen. For prescriptions of around-the-clock medications, adherence was 90%, but for medications that were to be taken on an as-needed basis, adherence was only 21%. Most patients reported moderate to severe pain the entire time. The most common reason for not taking analgesics was the unpleasantness of side effects.

VII. NOVEL THERAPIES FOR PAIN

Moderator: Michael Iadarola, PhD, Chief, Neurobiology and Pain Therapeutics Section, National Institute of Dental and Craniofacial Research Intramural Research Program

Conus Peptides: Discovering Diverse Non-Opioid Mechanisms for Alleviating Pain
Baldomero Olivera, PhD, University of Utah, Salt Lake City

Marine cone snails, of which there are 700 species, are all venomous and hunt fish, worms, or other snails. Their venom is highly potent and can kill humans with a 70% fatality rate. The active components of the venom are all small peptides. Each species of snail typically produces more than 100 different peptides, all with different modes of action. Furthermore, peptides produced by one species do not overlap with peptides produced by another. None of the toxins are opioids. All are highly specific for particular subtypes of receptors.

The cone snail toxins have been categorized into different functional groups termed cabals. Venomous peptides in the motor cabal bind to proteins at the neuromuscular junction and inhibit calcium channels, sodium channels, or the nicotinic acetylcholine receptor. One toxin purified from *Conus magus* selectively inhibits a specific type of calcium channel (CAV2.2), which is expressed by neuronal pain cells in the spinal cord. This toxin was developed by Neurex and is now marketed as Prialt, a drug for intractable pain that was approved by the FDA in December 2004. Toxins in a second cabal, the lightning strike cabal, all cause massive depolarization at the injection site, leading to a tonic-clonic type of seizure and to instant immobilization of the victim. Some of these peptides increase sodium channel conductance; others block potassium channels. In the third cabal, the nirvana cabal, toxins sedate the fish and put them into a very quiescent state. One of the venoms in the nirvana cabal binds a specific NMDA receptor and is currently being developed for epilepsy. Another is similar to neurotensin and is being developed for intractable pain.

A Neuronal Deletion Strategy for Pain Control

Michael Iadarola, PhD, Chief, Neurobiology and Pain Therapeutics Section, NIDCR

A toxin purified from latex secreted by the Moroccan plant *Euphorbia resinifera* has activity very similar to that of capsaicin, but it is 500 to 1000 times more potent. Resiniferia toxin binds to TRPV1, a membrane-bound sodium/calcium channel that is involved in sensing moderate heat pain. Overactivity of TRPV1 leads to cell death, due to the fact that TRPV1 is expressed not just on the cell surface but also on the endoplasmic reticulum (ER). When the channel is overactivated, the ER can no longer sequester calcium, calcium floods the interior of the cell, and this kills the cell in about 40 minutes. As a result, resiniferia toxin can be used to selectively kill the nociceptors that express TRPV1 on their surface. Injection of resiniferia toxin into the intrathecal space in rodents kills TRPV1 positive cells only, leaving other nerve cells intact.

Resiniferia toxin has been used to treat dogs with cancer pain or osteoarthritis. Injections of resiniferia toxin were made into the cisterna magna, allowing the toxin to percolate down the spinal cord and bind to and ablate TRPV1 positive cells. The injections were effective. Treated dogs were painfree and able to move around comfortably although the disease continued to progress. This approach is now going into Phase 1 clinical studies.

A New Technology for Measuring and Potentially Controlling Brain Activation

Associated with Pain: Real Time Functional Brain Imaging

Christopher deCharms, PhD, Omneuron, Menlo Park

To discover whether people can train their brains to control pain, normal subjects were placed in an MRI machine in front of a screen that displayed their brain activity in real time. Since converging information identifies the anterior cingulate cortex (aCC) as a brain structure important for pain perception, subjects were specifically shown the activity in their aCC and instructed to make the activity go up or down. A Peltier thermode was used to deliver thermal pain to the nondominant hand, and subjects were also instructed as to whether to attend to or attend away from the pain stimulus.

Activational control of the aCC increased over three training sessions. Although subjects were viewing only the cingulate cortex, review of the whole brain scans show that changes occurred everywhere in the pain network, including in the insular cortex, somatosensory cortex, medial thalamus, and cerebellum. After training, subjects also reported a difference in the amount of pain they felt from the thermal probe depending on whether they had increased or decreased activity in the aCC. Control subjects were shown activity that was not their own or was from a different brain region, and no increase in control over the aCC was observed.

In initial studies of 8 subjects with chronic pain, a substantial decrease in pain could be seen after one training session. The subjects said they had learned what they needed to do to cognitively control their pain. However, it was uniformly difficult for subjects to explain exactly what they were doing to change their brain activity. In a current long-term study, 21 subjects have been trained over six sessions. Statistically significant

decreases in chronic pain were observed which persisted for at least 1 week after the last training session.

VIII. JUNIOR INVESTIGATOR PRESENTATIONS

Moderator: Kathy Mann Koepke, PhD, National Institute of Nursing Research Pain Consortium Representative

Exercise-Induced Muscle Pain in Humans

Erin Dannecker, PhD, University of Missouri, Columbia

Eccentric contractions of muscle lengthens the muscle while it contracts, which leads to temporary deep muscle damage. In an experimental setting to examine this type of muscle damage, decreased pressure thresholds, loss of strength, and loss of motion and flexibility were observed concurrent with pain. These changes were frequently sufficient to interfere with the subjects' normal daily activities. The most common types of self-care were activity avoidance, stretching, and massage. About 30% of subjects also took over-the-counter analgesics. Recovery from this tissue damage results in muscle fibers that are more resistant to the same kind of damage. The relationship of inflammatory reactions caused by the tissue damage to pain and strength loss will need to be explored.

TNF Regulation of TRPV1 in Rat Trigeminal Neurons

Asma Khan, PhD, University of Texas Health Science Center, San Antonio

Tumor necrosis factor alpha (TNF α) is a proinflammatory cytokine that acts as a pain modulator. Receptors for TNF α co-localize with the sodium/calcium channel TRPV1 in a small number of nerve cells in the rat trigeminal ganglia. TNF α appears to directly alter the phenotype of primary sensory nerve cells. When cultures of rat trigeminal cells were exposed to TNF α , TRPV1 message was up-regulated as well as TRPV1 function [measured by release of the peptide CGRP or increase in intracellular calcium concentrations in response to capsaicin]. In the eye-wipe model of pain, application of TNF α for 30 seconds to the eye followed by application of capsaicin increased the period of time the animal spent wiping its eye compared to controls with no TNF α .

Modeling NRTI-Induced Allodynia in the Mouse

Susan Dorsey, PhD, University of Maryland, Baltimore

Nucleoside reverse transcriptase inhibitors (NRTIs) are widely used to treat HIV infections. Long-term treatment with these drugs can lead to the development of polyneuropathies, probably due to prolonged mitochondrial toxicity. To develop a model for NRTI-induced allodynia [where innocuous stimuli are now painful] the commonly used NRTI d4T was administered to mice by tail vein injection. Six days after injection, the mice appeared normal in many respects. There was no loss in body weight; grooming was normal; grip strength was unchanged; and voluntary running wheel performance was unaffected. However, the treated animals were allodynic. Hind paw withdrawal occurred at 0.16 gm rather than at 1 gm using graded von Frey filaments. Injection of MK801, a competitive antagonist of the NMDA glutamate receptor, reversed the allodynia.

Administration of brain derived neurotrophic factor, which regulates NMDA glutamate receptors, also reversed allodynia.